Wang, Shengjun 09/880,881

From: Hensle, Kristine (ASRC)
Sent: Thursday, November 03, 2005 10:15 AM
To: Wang, Shengjun
Subject: Litigation Search for U.S. Patent 5,556,838, Case: 09/880881

Good morning Mr. Wang, Litigation Search

I did not find any litigation for U.S. Patent No-5,556,838.

My steps:

1) I performed a KeyCite Search in Westlaw which retrieves all history on the patent including any litigation; none found. I attached the Derwent LitAlert Summary from Westlaw as well.
2) I performed a search on the patent in Lexis CourtLink for any open and closed dockets or closed cases; none found.
3) I performed a search in Lexis in the Federal Courts and Administrative Materials databases for any cases; none found.
4) I performed a search in Lexis in the IP Journal and Periodicals database for any articles on the patent; one found and attached.
5) I performed a search in Lexis in the news databases for any articles about the patent or any articles about litigation on this patent; none found.
6) I attached my screen captures to illustrate my search procedure.

If I can assist you further, please do not hesitate to contact me.

Best regards,

Kristine Hensle
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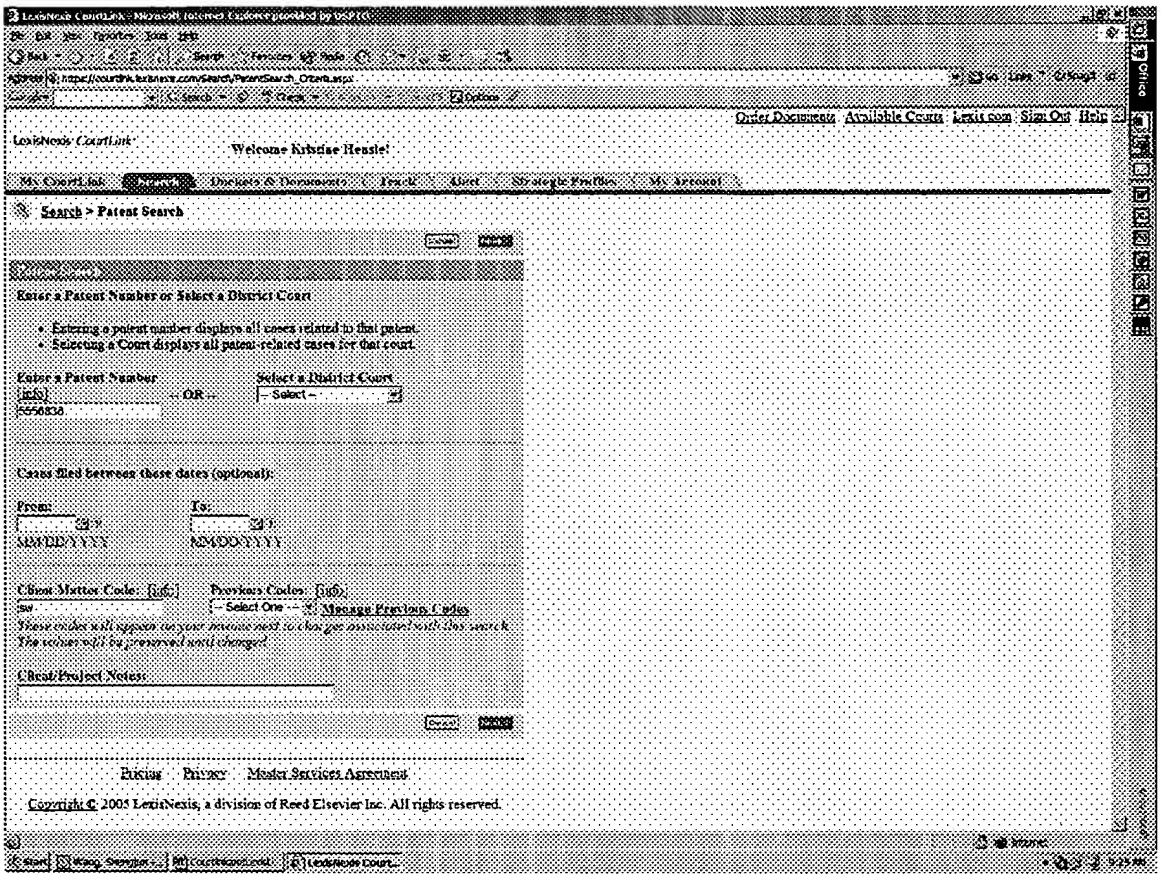
Courtlink and Lexis Litigation Search for U.S. Patent 5,556,838, Case: 09/880881.



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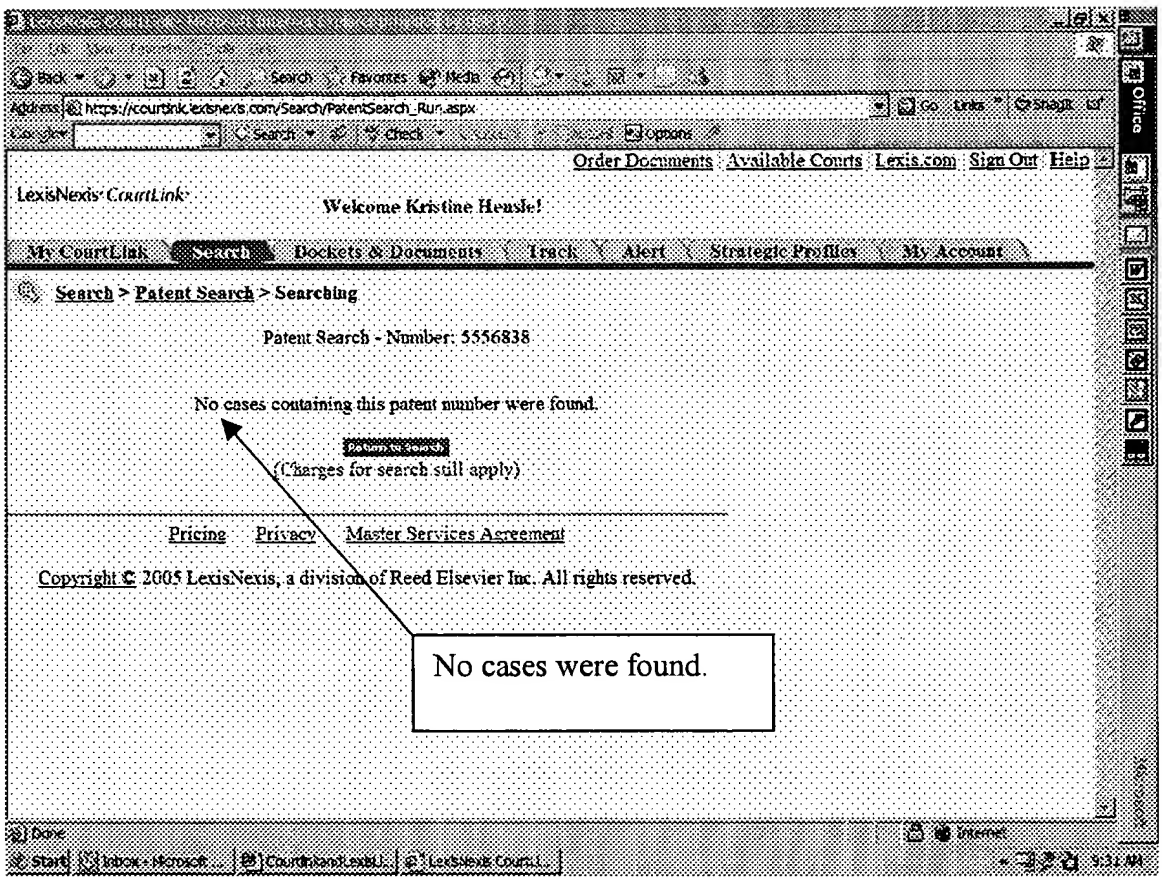
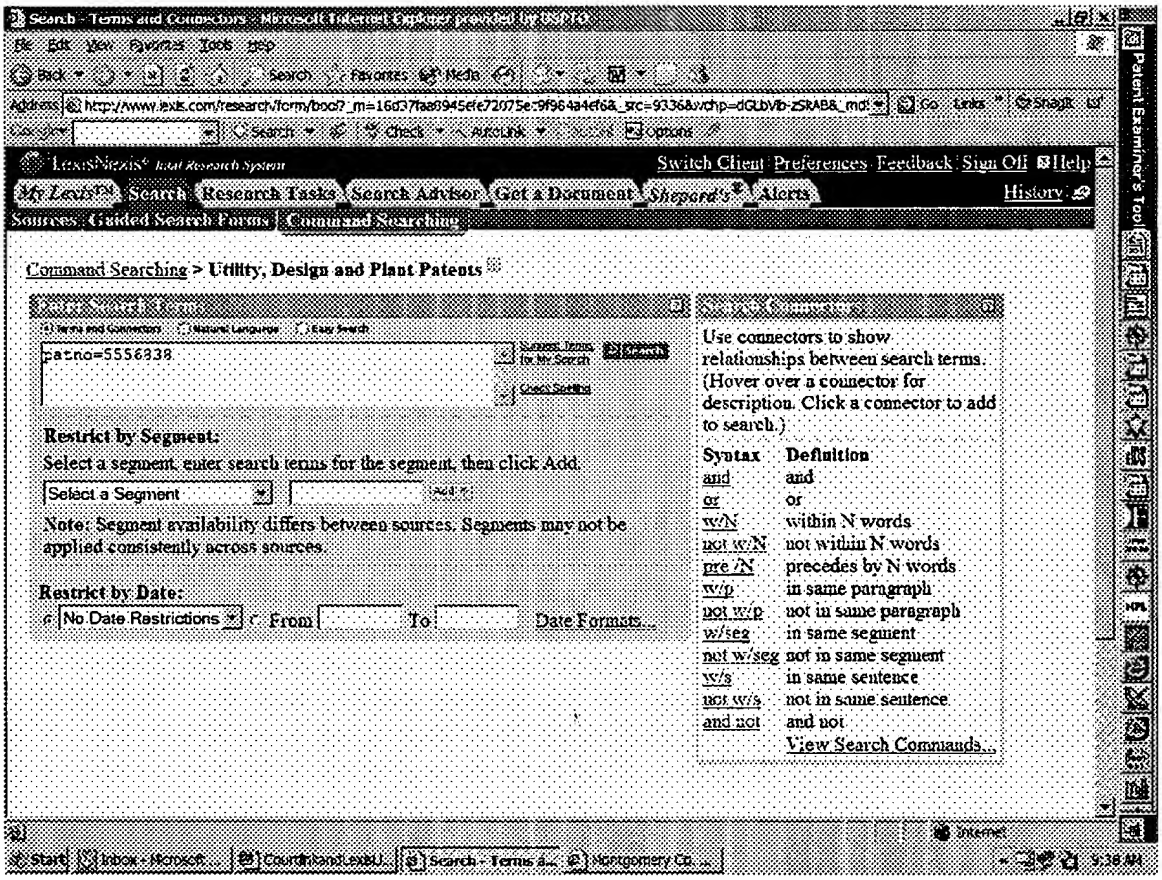


No cases were found.



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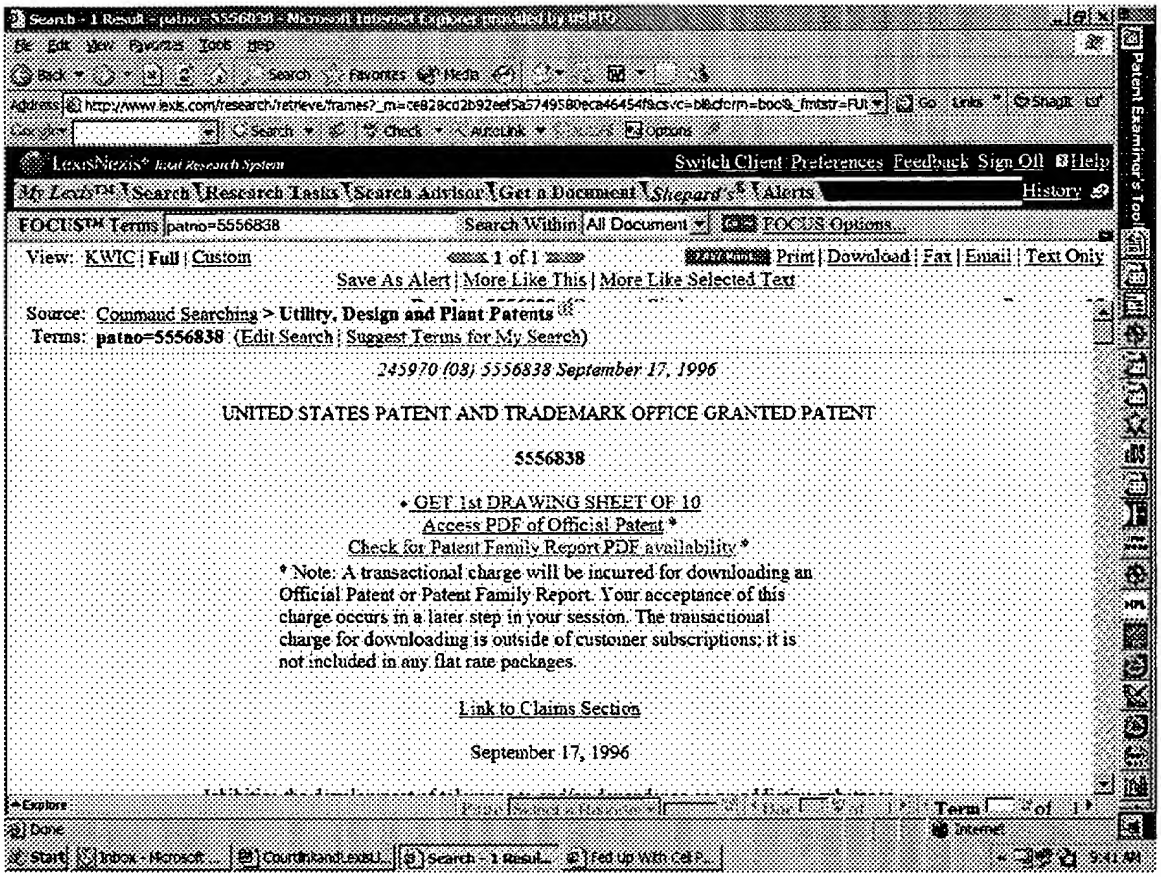

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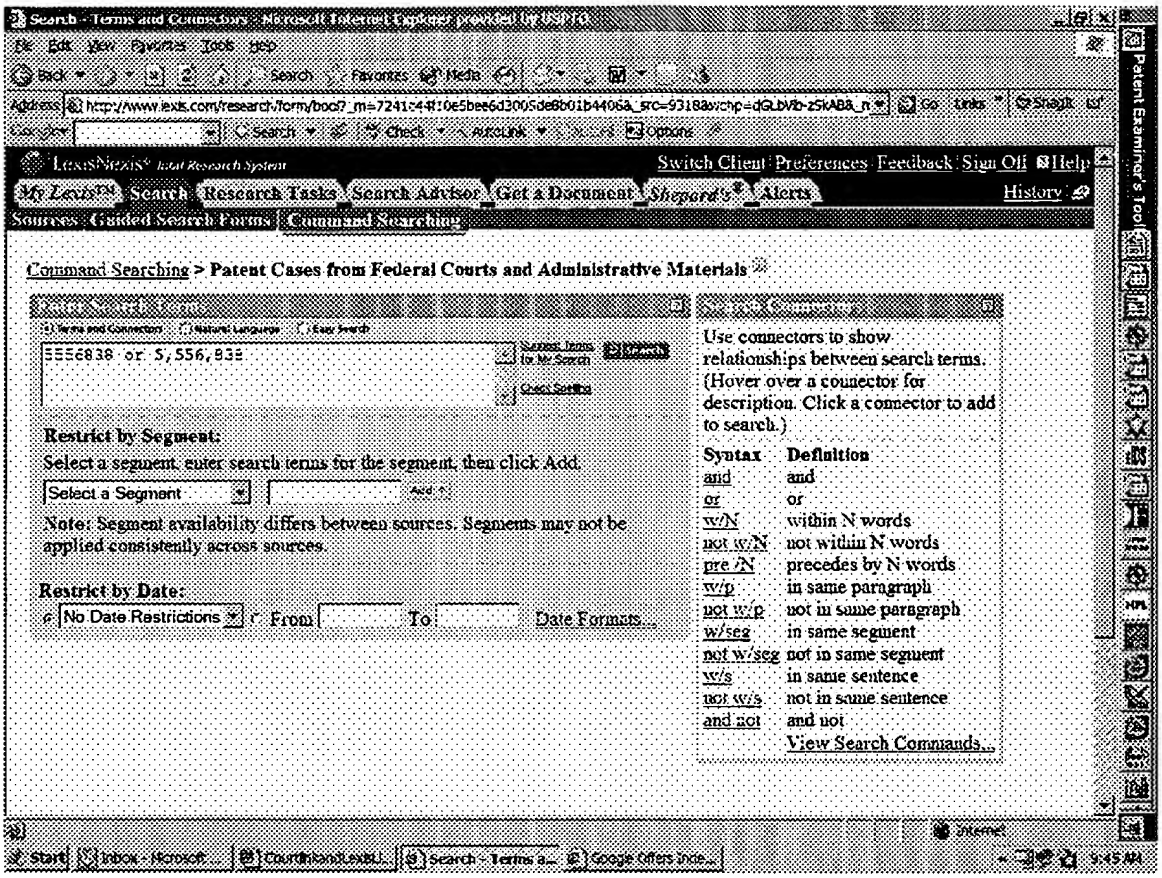

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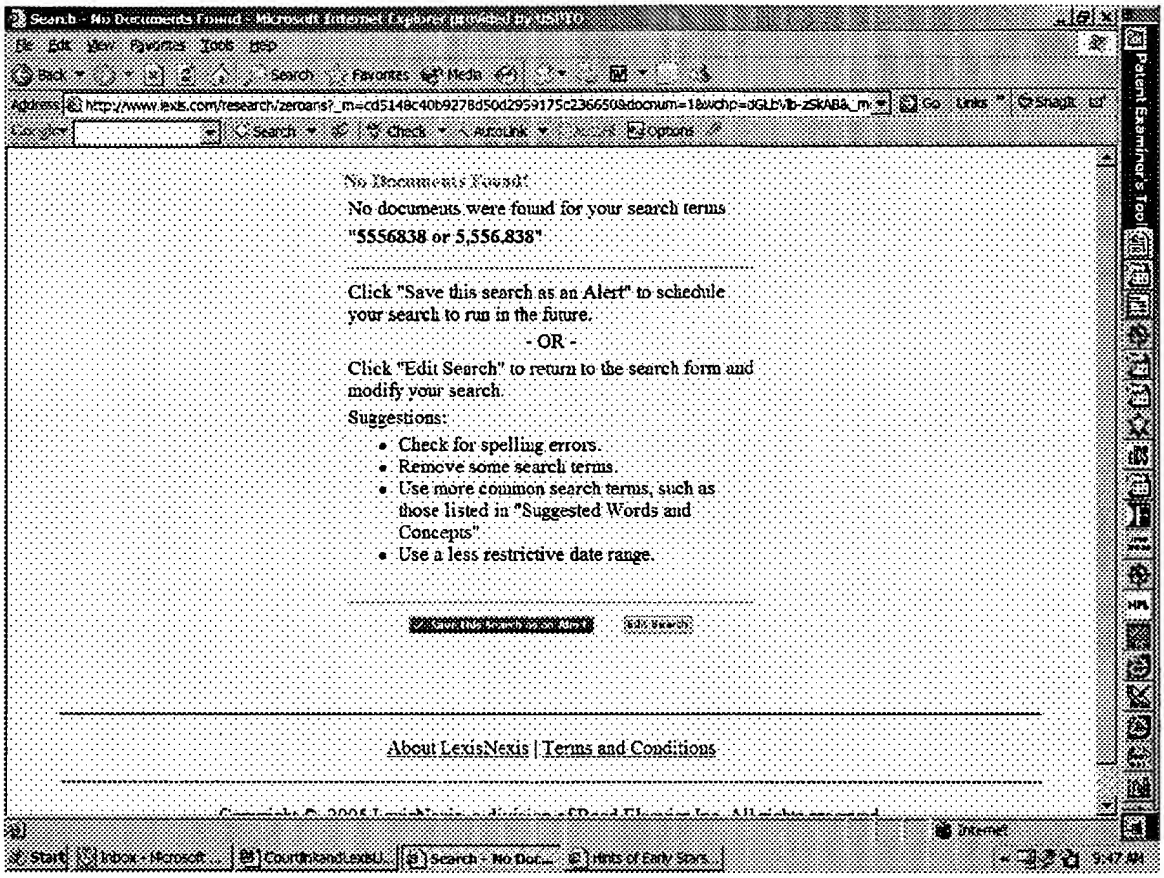

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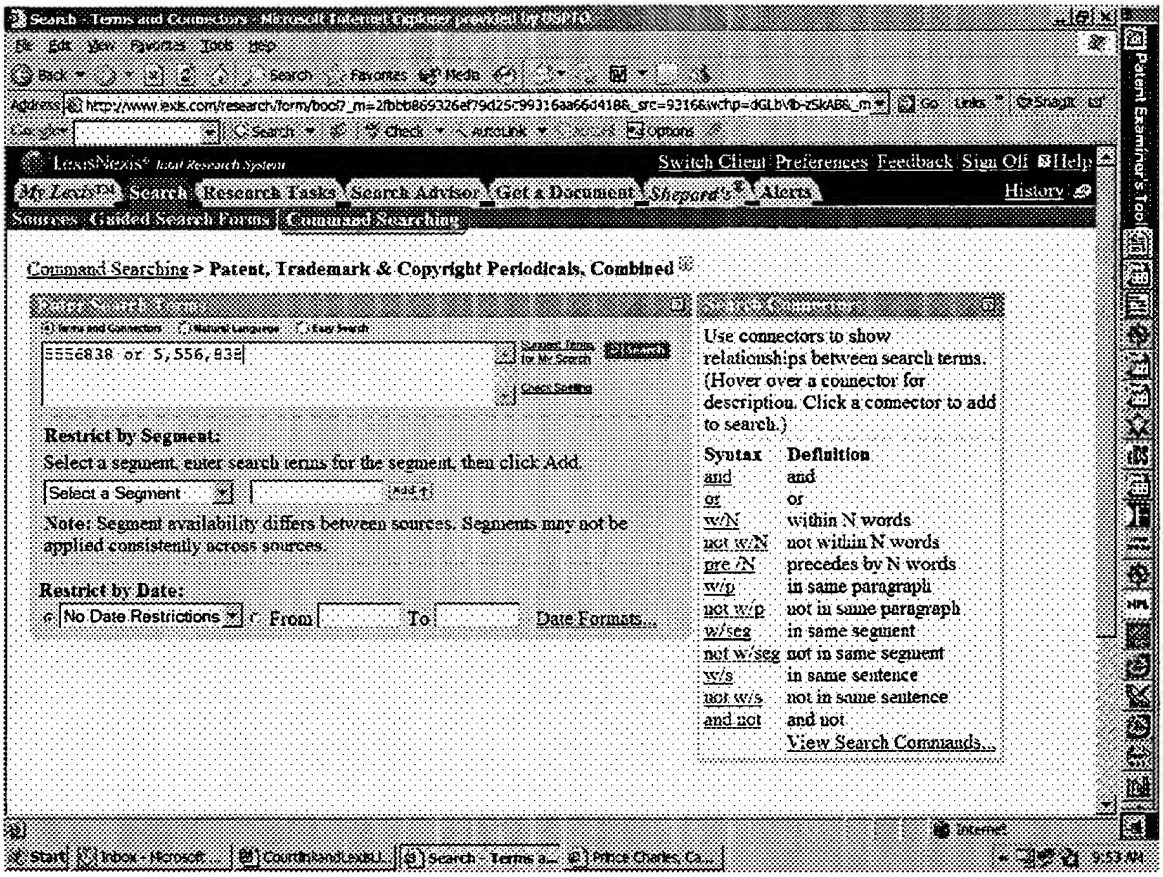

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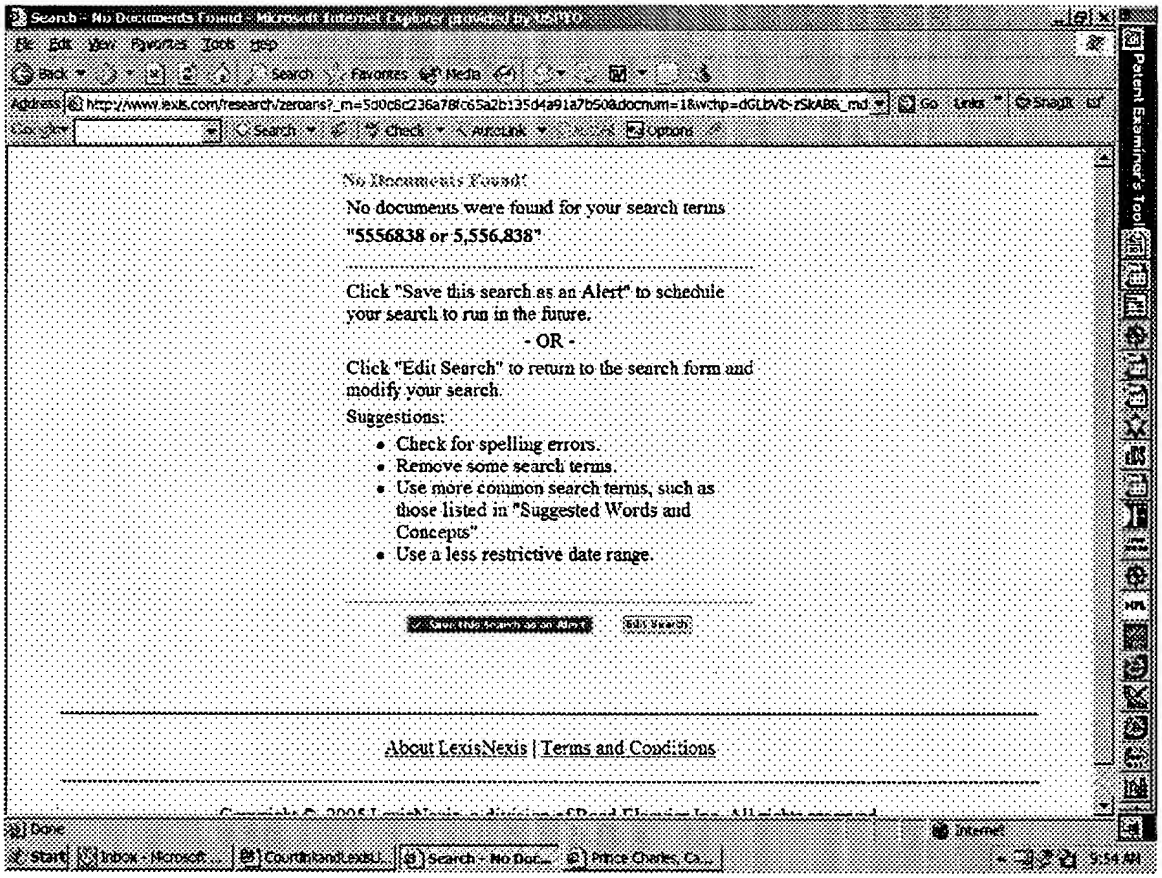

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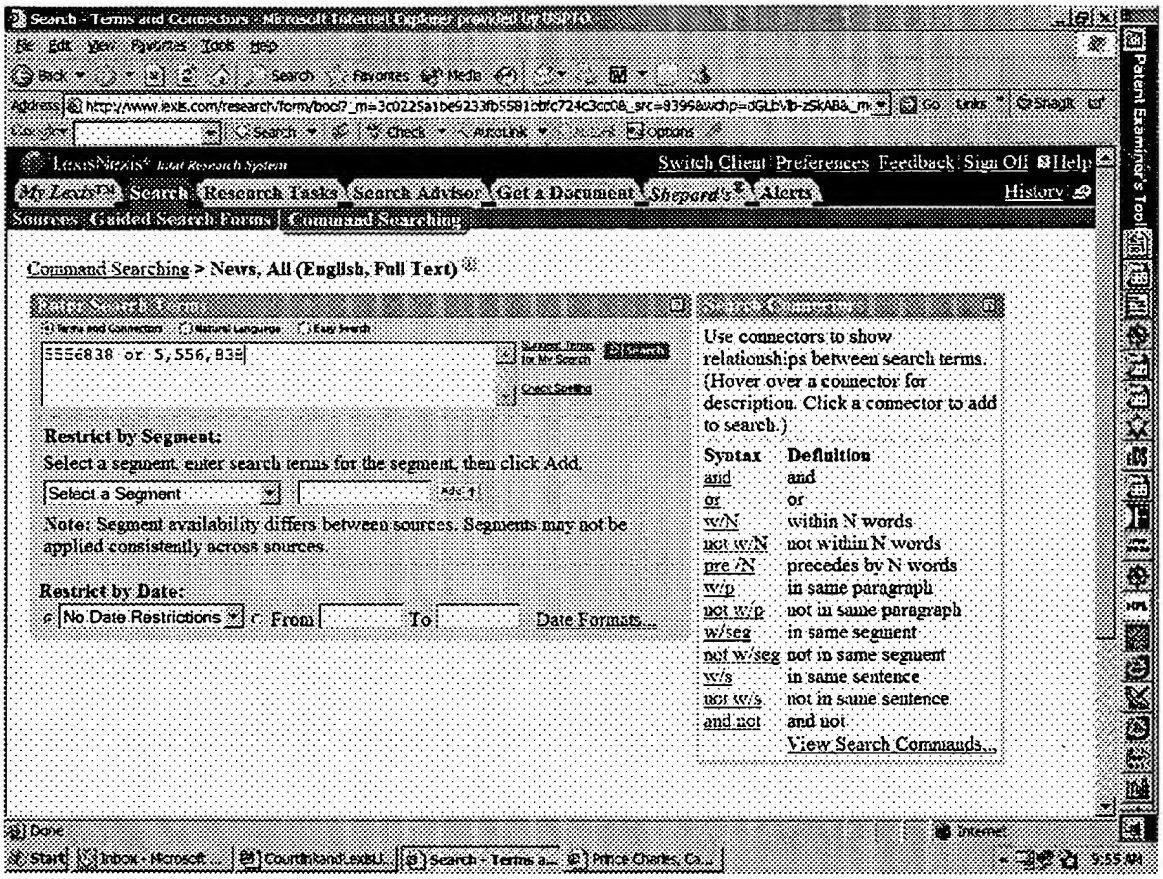
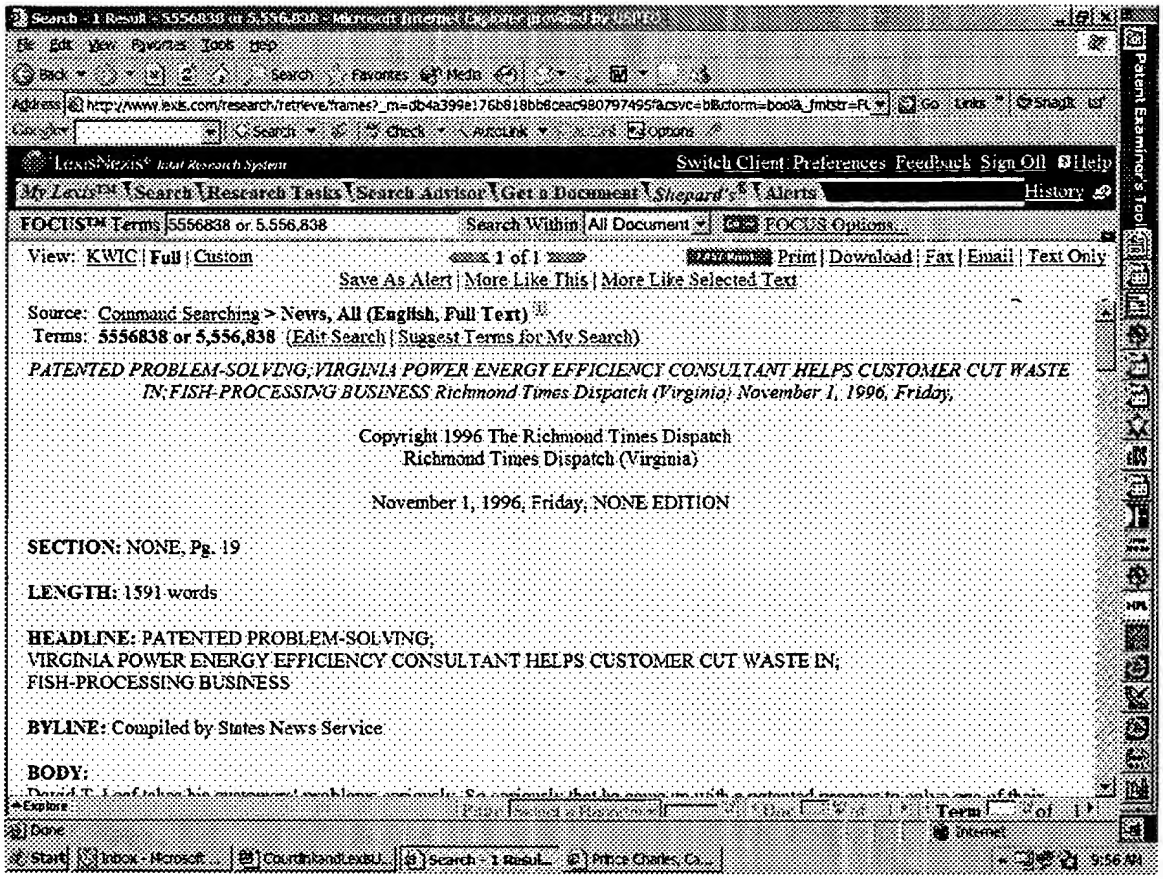


Searched the all news sources database.



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PATENTED PROBLEM-SOLVING; VIRGINIA POWER ENERGY EFFICIENCY CONSULTANT HELPS CUSTOMER CUT WASTE IN; FISH-PROCESSING BUSINESS Richmond Times Dispatch (Virginia) November 1, 1996, Friday,

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SECTION: NONE, Pg. 19

LENGTH: 1591 words

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VIRGINIA POWER ENERGY EFFICIENCY CONSULTANT HELPS CUSTOMER CUT WASTE IN;
FISH-PROCESSING BUSINESS

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BODY:

David T. Leaf takes his customers' problems seriously. So seriously that he came up with a patented process to solve one of their problems.

Problem-solving is part of the job for Leaf, who responds to customer inquiries as part of Virginia Power's energy efficiency group. However, the Richmonder had never landed a patent until recently.

Leaf devised a "chill separation system" that enables one of the power company's customers to reduce waste in his fish-processing business. Leaf came up with a cooling system that separates soluble fish proteins from wastewater. The fish proteins can then be used to make fish meal, which is sometimes fed to animals.

Leaf created the system a couple of years ago and decided to apply for a patent on the process. The patent was issued a couple of months ago.

Below is a list of other patents issued recently to Richmonders and people from throughout Virginia:

RICHMOND

Protective assembly for the steering ram of a marine outboard motor, Michael J. Gandarillas, Hopewell, patent number 5,556,310, filed Dec. 21, 1995.

Process of making and collecting continuous fibers in the form of a rod-shaped batt, Ashok H. Shah, Chesterfield, patent number 5,547,624, filed Aug. 9, 1994.

Method for fabricating a ballistic laminate structure, Andrew D. Park, Midlothian, patent number 5,547,536, filed Oct. 21, 1994.

Roll package convertible to a dispenser, Joseph F. Moore, Richmond, et. al, patent number 5,551,564, filed Feb. 2, 1994.

Conveyor system for rodlike articles, Albert D. Seim II, Richmond, Herman J. Steinbuchel, Richmond, Charles R. Willing, Richmond, patent number 5,556,236, filed June 7, 1995.

Preparation of near-neutral anionic salt feed minerals, William P. Moore, Hopewell, patent number 5,556,634, filed Apr. 13, 1995.

Inhibiting the development of tolerance to and/or dependence on an addictive substance, David J. Mayer, Richmond, Donald D. Price, Richmond, Jianren Mao, Richmond, patent number **5,556,838,** filed May 19, 1994.

Method and apparatus for filtering using filter mounted on tank partition wall, Solomon Schulzinger, Richmond, patent number 5,556,555, filed Jan. 20, 1995.

Computer picture toy for infants and very young children, Justin R. Cohen, Richmond, patent number 5,556,339, filed June 27, 1995.

Flat bed cart, Alan R. Kern, Richmond, John A. LaFleur, Richmond, George Hand, Midlothian, Bruce Ferris, Richmond, patent number 5,556,118, filed Jan. 5, 1995.

High strength composite, Leroy C.T. Lin, Richmond, Laura G. Wilson, Chester, Ashok Bhatnagar, Chester, et. al, patent number 5,552,208, filed Oct. 29, 1993.

Fabric securing device including adhesive and needle lubrication, Leo M. Moore, Richmond, patent number 5,546,877, filed June 10, 1994.

VIRGINIA

Apparatus which allows data sharing amongst computer program from different program environments, Marsha A. Brown, Manassas, Elaine S. Patry, Warrenton, William A. Remay, Warrenton, Kenneth M. Sissors, Centreville, et. al, patent number 5,557,776, filed Aug. 4, 1994.

System and method for data recovery, Steven B. Lipner, Oakton, et. al, patent number 5,557,765, filed Feb. 21, 1995.

Method and apparatus for display screens and coupons, Bruce R. DeWoolfson, Fairfax, patent number 5,557,721, filed Aug. 18, 1993.

System and method for centralized session key distribution, privacy enhanced messaging and information distribution using a split private key public cryptosystem, Ravi Ganesan, Arlington, patent number 5,557,678, filed July 18, 1994.

Channel interface unit, James P. Hogan, Sterling, et. al, patent number 5,557,672, filed March 10, 1993.

Channel interface unit, James P. Hogan, Sterling, et. al, patent number 5,557,670, filed Oct. 12, 1993.

Channel interface unit, James P. Hogan, Sterling, et. al, patent number 5,557,669, filed Oct. 12, 1993.

Handoff between overlay and underlay cells, Charles A. Barnett, Sterling, patent number 5,557,657, filed Sept. 9, 1993.

System and method for key escrow encryption, Steven B. Lipner, Oakton, et. al, patent number 5,557,346, filed Aug. 11, 1994.

Comestibles containing stabilized highly odorous flavor component delivery systems, Gerald E. Battist, Reston, Jose F. Zamudio-Tena, Vienna, et. al, patent number 5,556,652, filed Aug. 5, 1994.

System and method for applying a bladder release between a green tire and a bladder in a tire molding machine, Mike S. Coyne, Danville, Jim E. Newman, Ringgold, et. al, patent number 5,556,588, filed Jan. 6, 1995.

Filter assembly, Rex K. Ingalls, Virginia Beach, Harold H. Casey, Chesapeake, Rodger T. Moloney, Portsmouth, patent number 5,556,522, filed Sept. 2, 1994.

Process for cleaning large bone grafts and bone grafts produced thereby, Lloyd Wolfinbarger, Norfolk, patent number 5,556,379, filed Feb. 27, 1995.

Toilet lifting and transporting device, Ken Jacquay, Alexandria, patent number 5,556,076, filed April 6, 1995.

Necktie, Richard E. Ear, Herndon, patent number 5,555,563, filed June 7, 1995.

Customer premise device for controlling data transmissions by storing a limited number of operation algorithms and receiving operation instructions from external sources, Robert McLaughlin, Arlington, et. al, patent number 5,553,311, filed Feb. 17, 1994.

Method and apparatus for determining with high resolution the fidelity of information received on a communications channel, Stephen D., Harrison, Lynchburg, George D. Rose, Lynchburg, patent number 5,553,243, filed Jan. 7, 1994.

Methods of and apparatus for calibrating precisely spaced multiple transverse holographic gratings in optical fibers, Donald R. Lyons, Yorktown, et. al, patent number 5,552,882, filed March 28, 1995.

Method and system for displaying blended colors, Aaron M. Alpher, Ashburn, patent number 5,552,805, filed Nov. 25, 1995.

Measurement of topography using polarimetric synthetic aperture radar (SAR), Dale L. Schuler, Fairfax Station, Jong-Sen, Great Falls, patent number 5,552,787, filed Oct. 19, 1995.

High temperature copolymers from inorganic-organic hybrid polymers and multi-ethynylbenzenes, Teddy M. Keller, Alexandria, patent number 5,552,505, filed March 3, 1995.

Low dose oral contraceptives with less breakthrough bleeding and sustained efficacy, Gary D. Hodgen, Norfolk, patent number 5,552,394, filed July 22, 1994.

Positive resist composition containing naphthoquinonediazide compound having non-metallic atom directly bonded to the naphthalene ring, Daniel Bucca, Alexandria, et. al, patent number 5,552,256, filed Sept. 29, 1994.

Land based submarine weapons system simulator with control panel tester and trainer, Stephen G. Shaffer, Virginia Beach, Connie L. Thome, Virginia Beach, Timothy F. Clark, Chesapeake, patent number 5,551,875, filed Oct. 3, 1994.

End plate for railway crossties, scaffolding planks, and other wood products and methods of use, E. George Stern, Blacksburg, patent number 5,551,819, filed Dec. 29, 1994.

Retaining wall with an outer face and method of forming the same, Hubert J. Deaton III, Great Falls, et. al, patent number 5,551,810, filed June 8, 1994.

Cable storage and feeding device, Thomas D. Browning, Norton, patent number 5,551,647, filed June 10, 1994.

Conveyor with discontinuous turn, Quentin L. Wilson, Big Island, George H. Dawson III, Madison Heights, patent number 5,551,554, filed April 11, 1995.

Article combiner with multiple conveying surfaces and moving guides, William C. Crawford, Lynchburg, patent number 5,551,551, filed July 15, 1995.

Poultry nest pad cleaning method and apparatus, Derwood L. Runion, Timberville, patent number 5,551,460, filed Jan. 19, 1995.

Mounting adapter for air-assist fuel injector, Peter C. Rice, Yorktown, Anthony L. Franchitto, Hampton, Jingming J. Shen, Newport News, patent number 5,551,400, filed Dec. 18, 1995.

Method and apparatus for maintaining temperature control of sterile fluid, Durward I. Faries Jr., McLean, Mark Licata, Richmond, patent number 5,551,240, filed March 7, 1995.

Movable blade shaving cartridge with coated retaining clips, Frank H. Prochaska, Waynesboro, patent number 5,551,155, filed May 23, 1994.

Dual-mode booster system, Michael W. Evans, Forest, patent number 5,548,803, filed March 31, 1992.

System and method for adaptive active monitoring of high speed data streams using finite state machines, Paul C. Hershey, Manassas, patent number 5,548,775, filed Dec. 30, 1993.

Holographic structured light generator, Michael S. Massimi, Alexandria, William P. Blase, Alexandria, et. al, patent number 5,548,418, filed Sept. 12, 1995.

Electromagnetically actuated valve, Christopher Sortore, Charlottesville, et. al, patent number 5,548,263, filed June 28, 1993.

Method of producing foamed polymer materials, Donald K. Brandom, Blacksburg, Jose P. DeSouza, Blacksburg, Donald G. Baird, Blacksburg, Garth L. Wilkes, Blacksburg, patent number 5,547,996, filed July 29, 1994.

Fuel cell having uniform compressive stress distribution over active area, William R. Richards, Springfield, patent number 5,547,777, filed Feb. 23, 1994.

Method for preparing a topical, aminocaproic acid containing ophthalmic gel, Patricia B. Williams, Norfolk, Earl R. Crouch Jr., Virginia Beach, patent number 5,547,680, filed May 19, 1995.

Removing SO1/8x3/8, NO1/8X3/8 and CO from flue gases, Gerald J. Teitman, Vienna, et. al, patent number 5,547,648, filed May 5, 1995.

Method of using ultrasonic dental tool, Jack Goodman, Arlington, patent number 5,547,380, filed Aug. 19, 1994.

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United States Patent
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Patent Number: US 5556838

Document Type: Utility

Title: INHIBITING THE DEVELOPMENT OF TOLERANCE TO AND/OR DEPENDENCE ON AN ADDICTIVE SUBSTANCE

Issue Date: September 17, 1996 (19960917)

Inventor(s): Mayer, David J. (Richmond, VA); Price, Donald D. (Richmond, VA); Mao, Jianren (Richmond, VA); Lyle, John W. (Belmar, NJ)

Patent Assignee: Virginia Commonwealth University (Richmond, VA)

Application Number: 245970

Application Date: May 19, 1994 (19940519)

Related: Continuation of Ser. No. 43,280, April 06, 1993 (19930406), Pat. No. 5,321,012, which is a continuation-in-part of Ser. No. 10,583, January 28, 1993 (19930128), now abandoned.

International Class: [6] A61K-031/70; A61K-031/54; A61K-031/44; A61K-031/445

U.S. Class: 514/025; 514/216; 514/223.5; 514/225.5; 514/224.5; 514/282; 514/231.2; 514/304; 514/305; 514/306; 514/307; 514/812

Field of Search: 514/025; 514/304; 514/305; 514/306; 514/307; 514/216; 514/223.5; 514/225.5; 514/224.5; 514/282; 514/231.2; 514/812

REFERENCES CITED:

Other Publications:

Pharmacol. Biochem. Behav. vol. 35, No. 4 (1990), pp. 829-832.

Pharmacol. Biochem. Behav. vol. 43, No. 2 (1992), pp. 487-490.

Dtsch. Apoth.-Ztg. vol. 119, No. 21 (1979), p. 821, ""Opiat-Rezeptoren und Endorphine''.

Truillo et al.; ""Inhibition of Morphine . . . MIC801''; Science; vol. 251, pp. 84-87.

Marek et al; ""Brain Research, Delayed application of MIC801 . . . in rats.''; vol. 558, pp. 163-165.

Primary Examiner: Criares, Theodore J.

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Attorney/Agent/Firm: Dilworth & Barrese

ABSTRACT:

Nontoxic substances that block the N-methyl-D-aspartate (NMDA) receptor, e.g., a morphinan such as dextromethorphan or dextrorphan, or that block a major intracellular consequence of NMDA-receptor activation, e.g., a ganglioside such as GM subl or GT sublb , a phenothiazine such as trifluoperazine or a naphthalenesulfonamide such as N-(6-aminohexyl)-5-chloro-1- naphthalenesulfonamide, inhibit the development of tolerance to and/or dependence on addictive drugs, e.g., narcotic analgesics such as morphine, codeine, etc.

Claims: 2

Patent Pages: 16

Drawing Sheets: 10

CROSS REFERENCE TO RELATED APPLICATION

This is a continuation of application Ser. No. **08/043,280** filed Apr. **6, 1993**, now U.S. Pat. No. **5,321,012**, which is a continuation-in-part of U.S. patent application Ser. No. **08/010,583**, filed Jan. **28, 1993**, abandoned.

BACKGROUND OF THE INVENTION

This invention relates to a composition containing an addictive substance and a component which inhibits the development of tolerance to and/or dependence on the addictive substance. More particularly, the invention relates to a composition containing an addictive substance such as morphine or codeine and at least one nontoxic substance that blocks the N-methyl-D-aspartate (NMDA) receptor, e.g., a morphinan such as dextromethorphan or dextrorphan, or that blocks at least one major intracellular consequence of NMDA receptor activation, e.g., a ganglioside such as ganglioside GM subl or GT sublb , a phenothiazine such as trifluoperazine or a naphthalenesulfonamide such as N-(**6**-aminohexyl)-**5**-chloro-**1**-naphthalenesulfonamide.

Morphine is a rapid and effective drug for the treatment of severe pain but its long term administration has been limited due to its negative side effects, principally tolerance and dependence, which develop rapidly after administration. In an effort to make morphine of greater use in the treatment of pain, it has been combined with a variety of substances intended to inhibit one or more of its undesirable side effects. U.S. Pat. No. **2,770,569** describes the combination of morphine with the compound levo-d-hydroxy-N-allyl-morphinan which is said to suppress or eliminate such undesirable side reactions of morphine as depression, nausea and vomiting. U.S. Pat. No. **4,126,684** discloses reducing either the addiction liability of an addictive substance such as a narcotic analgesic or a barbiturate or the withdrawal symptoms caused by deprivation of such a substance in an addicted subject by administering the addictive substance, e.g., morphine, with a **4**-amino-**3**-p-halophenylbutyric acid. U.S. Pat. No. **4,415,871** describes the prevention of treatment tolerance and physical dependence in chronic morphine treatment by combining the morphine with any of the specific dipeptides indicated therein. U.S. Pat. No. **5,041,446** discloses inhibiting the development of tolerance to morphine by combining the morphine with dapiprazole. U.S. Pat. No. **5,057,519** achieves a reduction in morphine tolerance by combining the morphine with a benzamide antagonist for a subtype of the serotonin receptor, **5**-HT sub3. Trujillo et al., ""Inhibition of morphine tolerance and dependence by the NMDA receptor

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antagonist MK-**801''**, *Science*, **251** (**4989**), pp.

85-87, **Jan.** 4, 1991; **Tanganelli et al.,""Glutamate antagonists prevent morphine withdrawal in mice and guinea pigs'', *Neuroscience Letters*,** 122(2), **pp.** 270- 272, **Jan.** 28, 1991; **Marek et al.,""Excitatory amino acid antagonists (kynurenic acid and MK-** 801) **attenuate the development of morphine tolerance in the rat'', *Brain Research*,** 547(1), **pp.** 77-81, **Apr.** 26, 1991; **and, Marek et al., ""Delayed application of MK-**801 **attenuates development of morphine tolerance in rats, *Brain Research*,** 558(1), **pp.** 163-165, **Aug.** 30, 1991 **discuss the role of MK-**801 **(the compound** 5**-methyl-**10,11**-dihydro-SH-dibenzo[a,d]cyclohepten-**5,10**-imine), an NMDA receptor antagonist or blocker, in reducing morphine dependence in laboratory animals. However, MK-**801 **has been found to be toxic and is therefore unsuitable for pharmaceutical use.**

SUMMARY OF THE INVENTION

In accordance with the present invention, a composition is provided which comprises an addictive substance and at least one nontoxic substance that blocks the N-methyl-D-aspartate receptor or at least one major intracellular consequence of N-methyl-D-aspartate receptor activation.

Further in accordance with the present invention, a method of inhibiting the development of tolerance to and/or dependence on an addictive substance administered to a mammal which is liable to addiction thereto is provided which comprises administering the addictive substance to the mammal before, with or following administration to the mammal of a tolerance-reducing and/or dependence-reducing amount of at least one nontoxic substance that blocks the N-methyl-D-aspartate receptor or at least one major intracellular consequence of N-methyl-D-aspartate receptor activation.

Still further in accordance with this invention, a method of alleviating withdrawal symptoms in a mammal addicted to an addictive substance is provided which comprises administering to the addicted mammal the addictive substance before, with or following administration to the mammal of a dependence-reducing amount of at least one nontoxic substance that blocks the N-methyl-D-aspartate receptor or the intracellular consequences of N-methyl-D-aspartate receptor activation thereby alleviating withdrawal symptoms when the addictive substance is withdrawn from the mammal.

The term ""nontoxic'' as used herein shall be understood in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration (""FDA'') for administration to humans or, in keeping with established criteria, is susceptible to approval by the FDA for administration to humans.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1-10 are graphical representations of experimental data demonstrating the effectiveness of specific nontoxic substances that block the N-methyl-D-aspartate receptor or a major consequence of N-methyl-D-aspartate receptor activation for inhibiting morphine tolerance and dependence in rats.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

A particularly important category of addictive substances with which the present invention is concerned are the narcotic analgesics, e.g., opiates, opiate derivatives, opioids and their pharmaceutically acceptable salts. Specific examples

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of narcotic analgesics include alfentanyl, alphaprodine, anileridine, bezitramide, codeine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levorphanol, metazocine, methadone, metopon, morphine, opium extracts, opium fluid extracts, powdered opium, granulated opium, raw opium, tincture of opium, oxycodone, oxymorphone, pethidine, phenazocine, piminodine, racemethorphan, racemorphan, thebaine and pharmaceutically acceptable salts thereof. For a detailed discussion of these and other narcotic analgesics, reference may be made to Jaffe et al., ""Opioid Analgesics and Antagonists'' in

""Goodman and Gillman's Pharmacological Basis of Therapeutics'', Goodman et al., eds. 7th ed., **1985,** MacMillan and Company, New York pp. **491-531.**

Other addictive substances that can be utilized herein include acetorphine, acetyldihydrocodeine, acetylmethadol, allylprodine, alphracetylmethadol, alphameprodine, alphamethadol, benzethidine, benzylmorphine, betacetylmethadol, betameprodine, betamethadol, betaprodine, clonitazene, cocaine, codeine methylbromide, codeine-N-oxide, cyprenorphine, desomorphine, dextromoramide, diampromide, diethylthiambutene, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiamubutene, dioxaphetyl butyrate, dipipanone, drotebanol, ethanol, ethylmethylthiambutene, eton itazene, etorphine, etoxeridine, furethidine, hydromorphinol, hydroxypethidine, ketobemidone, levomoramide, levophenacylmorphan, methyldesorphine, methyldihydromorphine, morpheridine, morphine methylpromide, morphine methylsulfonate, morphine-N-oxide, myrophin, nicocodeine, nicomorphine, nicotine, noracymethadol, norlevorphanol, normethadone, normorphine, norpipanone, phenadoxone, phenampromide, phenomorphan, phenoperidine, piritramide, pholcodine, proheptazoine, properidine, propiran, racemoramide, thebacon, trimeperidine and the pharmaceutically acceptable salts thereof.

Still other addictive substances that can be utilized in the practice of the invention include the sedatives and hypnotics, e.g., benzodiazepines such as chlordiazepoxide, clorazepate, diazepam, flurazepam, halazepam, ketazolam, borazepam, oxazepam, prazepam, temazepam, triazolam and the pharmaceutically acceptable salts thereof, barbiturates such as amobarbital, ambobarbital, barbital, butabartital, mephobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, thiamylal and thiopental and the pharmaceutically acceptable salts thereof and other sedatives and hypnotics such as chloral hydrate, meprobamate, methaqualone, methyprylon and the pharmaceutically acceptable salts thereof.

By way of inhibiting the development of tolerance to and/or dependence on any of the foregoing and similarly addictive substances, the addictive substance is administered before, with or following the administration of at least one nontoxic substance that blocks the N-methyl-D-aspartate (NMDA) receptor or the intracellular consequences of N-methyl-D-aspartate receptor activation. Activation of the NMDA receptor, a subtype of excitatory amino acid receptors, induces a number of changes in the functional activity of nerve cells, and in particular, their capacity for excitability or inhibition in the presence of an addictive substance, via an increase in intracellular Ca++ concentration. The major consequences of NMDA receptor activation include the following sequences, or cascades, of events occurring within nerve cells: a) translocation and activation of protein kinases such as protein kinase C-->phosphorylation of substrate proteins such as cytosolic enzymes, channel proteins, receptor proteins, etc.-->changes in functional activity; b) initiation of early gene (c-fos, c-jun, zif-**268**, etc.) expression by either increased intracellular Ca++ or Ca++-activated protein kinases-->expression of functional genes responsible for production of cellular enzymes (such as protein kinases), receptor proteins (such as the NMDA receptor), ion channel proteins (such

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as K+, Na+, Ca++ channels), neuropeptides (such as dynorphin), etc.-->changes in functional activity; c) Ca++/calmodulin (or other Ca++ binding proteins) induced activation of enzymes and other cellular components-->activation of Ca++/calmodulin-protein kinase systems such as Ca++/calmodulin kinase II--> autophosphorylation of enzymes (e.g., Ca++/calmodulin kinase II) or other functional proteins-->changes in functional activity; d) Ca++/calmodulin induced activation of constitutive nitric oxide synthase as well as induction of inducible nitric oxide synthase-->production of nitric oxide-->i) production of cyclic guanosine monophosphate via activation of guanosine cyclase resulting in activation of protein kinases and early gene expression; ii) direct protein modification such as enzymes, receptor and/or channel proteins; iii) lipid membrane modification and/or nucleic acid modification via scavenge of free radicals; iv) induction of neurotoxicity at higher nitric oxide levels; v) retrograde actions in adjacent neurons or glial cells such as facilitation of glutamate release/NMDA receptor activation and/or inhibition of post-synaptic NMDA receptors-->changes in functional activity; e) interactions with the cyclic adenosine monophosphate/protein kinase A system, the phospholipase C-inositol triphosphate-Ca++-/diacylglycerol-protein kinase system, the phospholipase A2-arachidonic acid/prostanoids/leukotrienes system-->changes in functional activity induced by second messenger systems other than NMDA receptor/Ca++ /Ca++-calmodulin/protein kinase systems; and, f) interactions with other excitatory amino acid receptor subtypes including non-NMDA receptors and metabotropic receptors as well as intracellular events subsequent to the activation of these excitatory amino acid receptor subtypes-->changes in functional activity induced by the non-NMDA and metabotropic receptor activation.

A substance that blocks the NMDA receptor will effectively prevent all of the foregoing major intracellular sequences of events from taking place. However, even with activation of the NMDA receptor, it is still possible to inhibit the development of tolerance to and/or dependence on an addictive substance by combining the addictive substance with a substance that blocks at least one of the foregoing major intracellular sequences of events. Thus, e.g., a substance that interferes with translocation and activation of protein kinase C or with calmodulin induced activation of constitutive nitric oxide synthase as well as induction of inducible nitric oxide synthase is also useful for the practice of this invention.

Among the nontoxic substances that block the NMDA receptor and as such are useful in the practice of the present invention are morphinans such as dextromethorphan ((+) -3-hydroxy-N-methylmorphinan) and dextrorphan ((+)-3-hydroxy-N-methylmorphinan), their mixtures and the pharmaceutically acceptable salts thereof. Other useful nontoxic substances that block the NMDA receptor include ketamine (2-(2-chlorophenyl)-2-(methylamino)cyclohexanone), pyrroloquinoline quinone and cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid.

Nontoxic substances that block a major intracellular consequence of NMDA receptor activation and are therefore useful in the practice of the invention include inhibitors of protein kinase C such as the gangliosides, in particular, ganglioside GM subl (monosialoganglioside) and ganglioside GT sublb (trisialoganglioside); amphipathic long chain bases such as sphingosine, N,N,N-trimethylsphingosine, sphinganine and psychosine; quinolyloxazole-2 -ones such as 4 -methyl-5-(3-quinolinyl)-2-(3H)-oxazolone and phenyl-5-(2-quinolinyl)-2-3(3H)-oxazolone; 1,4-bis-(amino-hydroxyalkylamino)anthraquinones such as 1,4-bis-(3-propylamino-2-hydroxypropylamino)- 9,10 anthracenedione and 1,4 -bis-(3-benzylamino-

2-hydroxypropylamino)-9,10 anthracenedione; and, mixtures and pharmaceutically acceptable salts of any of the foregoing.

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Additional nontoxic substances that block a major intracellular consequence of NMDA receptor activation and as such are useful in the practice of the invention include inhibitors of calmodulin such as the phenothiazines, in particular, chlorpromazine, chlorpromazine sulfoxide, prochlorperazine dimaleate, perphenazine, trifluoperazine, fluphenazine, fluphenazine enanthate, fluphenazine decanoate, thioridazine, mesoridazine besylate, piperacetazine, acetophenazine dimaleate, carphenazine dimaleate, butaperazine dimaleate and phenothiazine sulfoxide; naphthalenesulfonamides such as N-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide, N-(6-aminohexyl)-5-chloro-2-naphthalenesulfonamide and

N-(6-aminohexyl)-5-bromo-2-naphthalenesul fonamide; 4 -substituted-4H,6H-pyrrolo[1,2-a][4,1] benzoxazepines such as 1,3-dihydro- 1-((1-[(4-methyl-4H,6 H-pyrrolo[1,2-a][4,1] benzoxazepin-4-yl)methyl]-4-piperidinyl)-2H-benzimidazol-2-one; benzhydryls such as N-[2] (diphenylmethylthioehtyl]-2-(trifluoromethyl)benzeneethanamine, N-[2 -(bis(4 -fluorophenyl)methylthio)ethyl]-2-(trifluoromethyl)benzeneethanamine and N-[2-(bis(4-fluorophenyl)methylthio)ethyl]-3 -(trifluoromethyl)benzeneethanamine; tricyclic antidepressant drugs such as imipramine, 2 -chloroimipramine and amitriptyline; penfluridol; haloperidol; pimozide; clozapine; calmidazolin; and, mixtures and pharmaceutically acceptable salts of any of the foregoing.

Administration of the composition of this invention can be in the form of a single dosage unit containing both the addictive substance and the nontoxic substance that blocks the NMDA receptor or a major intracellular consequence of NMDA receptor activation or the two substances can be administered separately provided both are ultimately present in effective amounts in the patient. Introduction of the composition into the patient can be by way of oral administration or by intravenous, intramuscular, subcutanous, intrathecal, epidural or intracerebroventrilcular injection.

The preferred dosage of addictive substance and the nontoxic substance that blocks the NMDA receptor or a major intracellular consequence of NMDA receptor activation can vary widely, e.g., from about **0.25** to about **250** mg/day, but actual amounts will vary according to the particular active substances being used, the particular formulation containing the active substances and tile state and circumstances of the host being treated. As those skilled in the art recognize, many factors that modify the action of the active substances herein will be taken into account by the treating physician such as the age, body weight, sex, diet and condition of the subject, the time of administration, the rate and route of administration, and so forth. Optimal dosages for a given set of conditions can be ascertained by those skilled in the art using conventional dosage determination tests in view of the experimental data provided herein.

In alleviating withdrawal symptoms in addicted subjects deprived of the addictive substance, the substance that blocks the NMDA receptor or a major intracellular consequence of NMDA receptor activation can be administered to the subject, together with the addictive substance, at a dosage rate of about **0.25** to about **250** mg/day, again, specific dosage levels and routes of administration being selected in accordance with the subject's circumstances. As a result of this treatment, the subject will experience a reduced level of dependence on the addictive substance eventually reaching the point where total withdrawal of the substance will result in at most mild withdrawal symptoms.

The composition herein can be formulated as a liquid, powder, elixir, injectable solution, etc. Formulations for oral use can be provided as hard gelatin capsules wherein the composition is mixed with an inert solid diluent such as calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the

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composition is mixed with an oleaginous medium, e.g., liquid paraffin or olive oil.

Aqueous suspensions can contain the composition in admixture with pharmaceutically acceptable excipients such as suspending agents, e.g., sodium carboxymethyl cellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrol idone, gum tragacanth and gum acacia; dispersing or wetting agents such as naturally occurring phosphatide, e.g., lecithin, or condensation products of an alkylene oxide with fatty acids, e.g., polyoxyethylene stearate, or condensation products of ethylene oxide with long chain al iphatic alcohols, e.g, heptadecaethyleneoxycetanol, or condensation products of ethylene exide with partial esters derived from fatty acids and a hexitol, e.g., polyoxyethylene sorbitol monoleate or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, e.g., polyoxyethylene sorbitan monooleate. Such aqueous suspensions can also contain one or more preservatives, e.g., ethyl- or n-propyl-p-hydroxy benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin or sodium or calcium cyclamate.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the composition in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, e.g., sweetening, flavoring and coloring agents, can also be present. Syrups and elixirs can be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations can also contain a demulcent, a preservative and flavoring and coloring agents.

The composition of this invention or either of its principal active ingredients can be provided in sustained release dosage form of which many kinds are known, e.g., as described in U.S. Pat. Nos. **4,788,055; 4,816,264; 4,828,836; 4,834,965; 4,834,985; 4,996,047; 5,071,646;** and, **5,133,974,** the contents of which are incorporated by reference herein.

The examples that follow are illustrative of the invention.

EXAMPLE **1**

The effect of systemic dextrorphan on prevention of the development of morphine tolerance and dependence was examined in Sprague-Dawley rats weighing **350-400** gm. Morphine tolerance was developed in the rats by twice daily subcutaneous injection of **10** mg/kg morphine sulfate. The analgesic effect of the morphine was examined by using the well known tail-flick test which measures the latency of tail-flick upon radiant heat stimulation. The latency of tail-flick test is defined as the time elapsed from the onset of radiant heat to the flick of the rat's tail. In order to examine the effect of dextrorphan on the development of morphine tolerance, each morphine-treated rat also received intraperitoneal administration of either dextrorphan (**1.56, 3.13, 6.25, 12.5** mg/kg, n = **5**/group) or saline (n = **6**) given **30** minutes prior to each morphine administration.

FIG. 1 shows the effects of systemic doses of dextrorphan (DEX) on tolerance to morphine analgesia produced by twice daily subcutaneous administration of **10** mg/kg morphine. Each symbol represents mean tail-flick latency scores (those above **4.5** seconds reflect analgesia) for each group of rats (N = **5-6**) and vertical bars are standard errors in this and the other figures. Baseline scores were between **4** and **5** seconds (at Day **0**) and post-drug scores measured **1** hour after drug administration were close to **10** seconds for the first **5** days of daily drug administration. The control group (open triangles) show marked reduction in response to morphine (i.e.,

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tolerance) at **7** and **9** days. In contrast, dextrorphan potently prevented the development of morphine tolerance as shown by no significant decreases in tail flick latencies, i.e., remaining analgesic during the whole course of repeated morphine administration. Asterisks indicate mean scores that were significantly different from those of the control group. All tested doses of dextrorphan were effective in preventing development of morphine tolerance with optimal doses ranging from **3.13** mg/kg to **12.5** mg/kg.

FIG. 2 shows the effects of systemic doses of dextrorphan on jumping, a withdrawal symptom produced by subcutaneous naloxone (**2** mg/kg) in rats previously injected with morphine (**10** mg/kg) twice daily for **9** days. Asterisks indicate median number of jumps in dextrorphan treatment groups (MOR+DEX) that were significantly less than that of the control group (MOR+SAL). Vertical bars refer to the range of the numbers of jumps. Thus, **3.13** and **6.25** mg/kg dextrorphan (but not

1.56 mg/kg) significantly reduced the incidence of jumping in morphine tolerant rats, a behavioral manifestation of morphine dependence, brought about following subcutaneous injection with **2** mg/kg naloxone. Thus, coadministration of dextrorphan with morphine greatly inhibits the development of both tolerance to and dependence on morphine while the analgesic effect of the morphine remains substantially unaffected.

EXAMPLE **2**

The effects of ganglioside GM subl in inhibiting morphine tolerance and dependence utilizing both systemic and intrathecal treatment were evaluated. The systemic treatment procedure, including both morphine and ganglioside GM subl administration, was exactly the same as that used in the experimental work presented in Example **1** except that ganglioside GM subl was given **1** hour before each morphine administration.

As shown in FIG. 3, the tail flick latency in ganglioside GM sub 1 -treated (**10, 30, 60** mg/kg, n = **6**/group) rats remained significantly longer than that of saline-treated rats on days **5, 7, 9** and **10** of repeated morphine administration, indicating the prevention of the development of morphine tolerance by ganglioside GM1. Although all **3** doses of ganglioside GM subl were effective, **30** and **60** mg/kg were more effective at days **9** and **10** than **10** mg/kg.

FIG. 4 shows the effects of systemic doses of ganglioside GM subl on jumping, a withdrawal symptom produced by subcutaneous naloxone (**2** mg/kg) in rats previously injected with morphine (**10** mg/kg) twice daily for **9** days. Asterisks indicate median number of jumps in GM subl treatment groups (M+G) that were significantly less than that of the control group (MOR+SAL). Vertical bars refer to the range of the numbers of jumps. All three doses [**10** mg/kg (**10**); **30** mg/kg (**30**); **60** mg/kg (**60**)] of GM subl were effective with **60** mg/kg GM subl being the most effective dose tested.

EXAMPLE **3**

This example demonstrates the effectiveness of ganglioside GM subl in preventing the development of morphine tolerance at the site of the spinal cord. Morphine sulfate **10** <<mu>>g was delivered once daily through an intrathecal (spinal) canula implanted **5** days before the first morphine injection. Ganglioside GM subl or saline also was delivered intrathecally **30** minutes before each morphine injection.

FIG. 5 shows the effects of the intrathecal doses of ganglioside GM subl on tolerance to morphine analgesia produced by once daily intrathecal administration of **10** <<mu>>g morphine. Intrathecal ganglioside GM subl was given **30** min before

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each morphine administration. Each symbol represents mean scores for maximal possible effects (and hence analgesia) for each group of rats (n = **5-6**) measured at **15, 30, 60, 90, 120, 180,** and **240** minutes after morphine injection on Day **8,** i.e., **24** hours following **6** consecutive daily intrathecal morphine injections. Vertical bars are standard errors. Maximal possible effects (MPE) were calculated by the formula % MPE

= [(TL - BL)/(**10** - BL)] x **100.** TL: actual tail-flick latency; BL: baseline latency obtained before the first morphine injection; **10:** cut-off time for radiant heat stimulation. The control group (open circle) showed marked reduction in response to morphine (i.e., tolerance) at each tested time point. In contrast, treatment with ganglioside GM subl effectively prevented the development of morphine tolerance as indicated by significantly higher maximal possible analgesia effects of morphine (**160** nmol>**80** = **40** nmol) as compared to those of saline-treated rats. Asterisks indicate mean scores that were significantly different from those of other groups.

EXAMPLE **4**

The effects of ganglioside GM subl and the toxic NMDA receptor antagonist MK **801** on morphine tolerance were evaluated.

As shown in FIG. 6, treatment with ganglioside GM subl (**60** mg/kg) inhibited the development of morphine tolerance to the degree equivalent to that induced by **0.3** mg/kg MK **801.** However, **50%** (**3** out of **6**) of the rats treated with **0.3** mg/kg MK **801** died before the completion of the experiment and the remaining rats in the group showed apparently poor grooming and weight loss indicating adverse effects of MK **801** on health. The rats treated with ganglioside GM subl or dextrorphan continued to appear well groomed and did not show weight loss. None of the rats in the GM subl or dextrorphan treatment groups died due to drug administration. Thus, dextrorphan and GM subl are nontoxic in contrast to MK **801** which exhibits severe cytotoxic effects and as such, is unlikely to be approved by the FDA for administration to humans.

EXAMPLES **5** AND **6**

These examples illustrate the effects of the phenothiazine trifluoperazine (Example **5**) and the naphthalenesulfonamide N-(**6**-aminohexyl)-**5**-chloro-**1**-naphthalenesulfonamide hydrochloride (Example **6**) in preventing the development of morphine tolerance in rats.

Calmodulin is an intracellular colactor necessary for the nitric oxide pathway that can be initiated upon NMDA receptor activation. FIGS. 7-10 demonstrate that trifluoperazine (TFP) and N-(**6**-aminohexyl)-**5**-chloro-**1**-naphthalenesulfonamide hydrochloride (W-**7**), both of which are calmodulin antagonists, effectively prevent the development of morphine tolerance in rats following intrathecal administration. In both cases, rats receiving once daily morphine sulfate (**10** <<mu>>g) and saline injection given intrathecally for **7** consecutive days developed tolerance to the analgesic effect of morphine as indicated by the reliable decrease in tail-flick latencies as compared to baseline latencies (day **1**). In contrast, rats treated with TFP or W-**7** (**100** or **50** nmol) given immediately before each morphine administration showed a reliable analgesic effect of morphine (day **8**) employing the same dose regimen used in the saline treatment group. The prevention of the development of morphine tolerance by TFP or W-**7** is dose-related: **100** = **50** nmol>**25** = **12.5** nmol. Each data point in FIGS. 7-10 represents the mean of a group of rats (n = **6**) and standard errors are shown by vertical lines. The asterisks refer to statistical differences (<<ALPHA>> = **0.05**) between the saline group and each other group.

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What is claimed is:

1. A composition comprising an addictive substance and at least one nontoxic substance that blocks the N-methyl-D-aspartate receptor or a major intracellular consequence of N-methyl-D-aspartate receptor activation, the addictive substance being selected from the group consisting of alfentanyl, alphaprodine, anileridine, bezitramide, codeine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levorphanol, metazocine, methadone, metopon, morphine, opium extracts, opium fluid extracts, powdered opium, granulated opium, raw opium, tincture of opium, oxycodone, oxymorphone, pethidine, phenazocine, piminodine, racemethorphan, racemorphan and pharmaceutically acceptable salts thereof.

2. The composition of claim 1 in sustained release dosage form.

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Date of Printing: NOV 03,2005

KEYCITE

C US PAT 5556838 INHIBITING THE DEVELOPMENT OF TOLERANCE TO AND/OR DEPENDENCE ON AN ADDICTIVE SUBSTANCE, Assignee: Virginia Commonwealth University (Sep 17, 1996)

History

=> 1 **INHIBITING THE DEVELOPMENT OF TOLERANCE TO AND/OR DEPENDENCE ON AN ADDICTIVE SUBSTANCE,** US PAT 5556838, 1996 WL 1439644 (U.S. PTO Utility Sep 17, 1996) (NO. 245970)

Assignments

2 Assignee(s): VIRGINIA COMMONWEALTH UNIVERSITY MEDICAL COLLEGE OF VIRGINIA1200 EAST MARSHAL STREET RICHMOND, VIRGINIA 23298, DATE RECORDED: Apr 06, 1993

Patent Status Files

. Reissue Application Filed, (OG date: Aug 21, 2001)

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KEYCITE

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